REMARKS

Claims 1, 12, 14, 18-20 and 25 have been amended. Claims 13 and 28-31 have been cancelled without prejudice. Claims 5-6, 15-17, 23 and 27 were previously canceled. Subsequent to the entry of the present amendment, claims 1-4, 7-12, 14, 18-22 and 24-26 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendment to the Claims

Claims 1, 12, 18-20 and 25 have been amended to recite, in part, that "the specimen [or tissue] appears histologically normal".

Support for the amendments is found in the application as filed, for example: "... a primary tumor is detectable in the adjacent histopathologic surgical margins and more distant tissues, such as regional lymph nodes, which are apparently "normal" when examined by standard histological techniques (page 4, lines 2-6)". The specification also describes tumor margins which are "histologically negative for tumor" (page 48, line 27; page 49, line 6 and line 9; FIG.3); and lymph nodes which were "histologically negative" (page 35, lines 5-6; page 49, line 23).

Thus, all amendments to the claims are fully supported by the specification and original claims and no new matter has been added.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-4, 7-11, 20-22, 24-26, and 28-31 are rejected under 35 U.S.C. §112, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 28-31 have been cancelled, thus the rejection with regards to these claims is moot. Applicant traverses the rejection of the other pending claims as it may apply to the amended claims.

According to the Office Action, the phrase "does not exhibit microscopic characteristics indicative of neoplastic pathology" is allegedly not defined in the specification or the art.

Claims 1, 12, 18-20 and 25 have been amended to recite, in part, that "the specimen [or tissue] appears histologically normal". The amendment is fully supported in the specification, as discussed above. Thus, it is submitted that the claims point out and distinctly claimed the subject matter which Applicant regards as the invention.

Accordingly, withdrawal of rejection of claims 1-4, 7-11, 20-22, 24-26, and 28-31 under 35 U.S.C. §112, second paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §112, First Paragraph (written description/new matter)

Claims 1-4, 7-11, 20-22 and 24-26 are rejected under on 35 U.S.C. §112, first paragraph as allegedly not containing a written description of the invention and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to practice the method in its best mode. Applicant respectfully traverses the rejection as it applies to the amended claims.

According to the Office Action, the phrase "does not exhibit microscopic characteristics indicative of neoplastic pathology" is allegedly not sufficiently described in the specification.

Claims 1, 12, 18-20 and 25 have been amended to recite, in part, that "the specimen [or tissue] appears histologically normal". As discussed above, there is sufficient support in the specification as filed for the amendment and no new matter has been added. As such, the amendment to the claims is sufficiently described in the application as filed.

Accordingly, withdrawal of rejection of claims 1-4, 7-11, 20-22 and 24-26 under 35 U.S.C. §112, first paragraph is respectfully requested.

IV. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 1-4, 7-14, 18-22 and 24-26 are rejected under on 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Claim 13 has been canceled, thus the rejection with regards to this claim is moot. Applicant respectfully traverses the remainder of the rejection as it applies to the amended claims.

According to the Office Action it is "completely unpredictable as to whether said nucleic acids may in fact be detected by the methods of the claims in the samples having 'no microscopic characteristics indicative of neoplastic pathology'". However, the Office Action admits that, "[i]n the instant case, *the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant may be detected*"; see page 7 of the Office Action.

Claims 1, 12, 18-20 and 25 have been amended to recite, in part, that "the specimen [or tissue] appears histologically normal". As discussed above, there is sufficient support in the specification as filed for the amendment.

The application describes that adjacent histopathologic surgical margins and more distant tissue such as regional lymph nodes, appear "normal" when examined by standard histopathological methods (see page 4, lines 1-16; and page 8, lines 2-7, and page 9, lines 1-6). The specification also describes that specimens of the surgical margins, which remain in the patient following excision of a primary tumor (page 35, lines 15-21), or remaining lymph nodes (page 36, lines 2-4), can be obtained, and examined by standard procedures such as hematoxylin and eosin staining or using a probe specific for a target nucleic acid (page 36, lines 5-15; and page 39, line 13, to page 44, line 21). Therefore, the claimed invention is *not* "completely unpredictable".

Further, in the amendment filed July 23, 2004, Applicant stated that (paragraph bridging pages 8 and 9):

> The skilled artisan, viewing the subject application, reasonably would have known that the claimed methods could be practiced with respect to the presently recited mutant nucleic acids (i.e., APC, DCC, etc.) because it was well known at the time the subject application was filed that mutations of the recited genes, like p53 mutations, occur in a variety of metastatic cancers (see, e.g., Table 1, page 11). More specifically, Applicant's disclosure that mutant p53 nucleic acid present in metastatic tumor cells can be detected in tissues that appear histologically normal (e.g., tumor surgical margin and lymph nodes) *provides the general teaching that tumor cells that metastasize from a primary tumor can be identified in otherwise normal appearing tissues by detecting the mutant target nucleic acid present in the primary tumor cells.* Thus, based on this disclosure, as exemplified using p53 mutations, the skilled artisan would have known that metastatic tumor cells having mutations of the recited genes similarly could be detected in histologically normal tissue such as lymph nodes and tumor margins.

Thus, one skilled in the art reviewing the instant application is more than able to make and use the claimed the invention.

Also, according to the Office Action, "no quantity of experimentation would actually be sufficient to enable the practice of the claimed invention (page 9 of the Office Action)".

MPEP §2164.06 states that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a *reasonable amount of guidance with respect to the direction in which the experimentation should proceed* (emphasis added)". *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

It is submitted that the specification provides a "reasonable amount of guidance with respect to the direction in which the experimentation should proceed". The specification describes "histopathologic surgical margins, lymph nodes and oral cavity swabs from at least twenty patients (page 25, lines 1-2)"; Example 2 describes the claimed invention with regards to a tumor margin (claim 1); Examples 2 and 4 with regards a surgical margin (claim 12), and

Example 4 with regards to lymph nodes (claim 20). Thus, as stated in MPEP §2164.06, the test is "not merely quantitative" so long as the specification is "reasonable... with respect to the direction in which the experimentation should proceed".

Accordingly, withdrawal of rejection of claims 1-4, 7-14, 18-22 and 24-26 under 35 U.S.C. §112, first paragraph is respectfully requested.

V. Rejections under 35 U.S.C. § 102

Claims 28-30 are rejected under 35 U.S.C. §102(a) for being allegedly anticipated by Nees et al. (1993; hereinafter, "Nees"). Claims 28 to 30 have been canceled, thus the rejection with regards to these claims is moot.

Accordingly, withdrawal of rejection of claims 28-30 under 35 U.S.C. § 102, first paragraph is respectfully requested.

VI. Rejections under 35 U.S.C. § 103

A. Claim 31

Claim 31 is rejected under 35 U.S.C. §103(a) for being allegedly obvious over Nees. Claim 31 has been canceled, thus the rejection with regards to this claim is moot.

B. Claims 12 and 18-19

Claims 12 and 18-19 are newly rejected under 35 U.S.C. §103(a) for being allegedly obvious over Nees in view of Hamilton (1992; hereinafter "Hamilton"). Applicants respectfully traverse the rejection as it applies to the amended claims.

According to the Office Action, Nees discloses that mutated p53 nucleic acids were detected in tumor-adjacent and tumor distant specimens having no neoplastic morphology (page 12-13 of the Office Action). Further, that although Nees does not disclose any mutated forms of

APC, DCC, NF1, NF2, RET, VHL, and WT-1, Hamilton discloses that "APC and DCC" are found in altered colorectal carcinomas (page 12 of the Office Action). Hence, according to the Office Action, an ordinary artisan would have modified the methods of Nees to assay the genes disclosed by Hamilton (page 12 of the Office Action).

Claims 12 and 18-19 have been amended. Applicants submit that the combination of Nees and Hamilton does not disclose the claimed invention, as neither reference discloses the *mutant* neoplastic nucleic acids of APC, DCC, NF1, NF2, RET, VHL, and WT-1 (Table 1, page 11) in histologically normal specimens. Furthermore, the Office Action admits that, "[i]n the instant case, *the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant may be detected*"; see page 7 of the Office Action. Thus, claims 12 and 18-19 are rendered unobvious over Nees in view of Hamilton.

C. Claim 13

Claim 13 is rejected under 35 U.S.C. §103(a) for being allegedly obvious over Nees in view of Hamilton and further in view of Sobol et al. (U.S. Patent No. 5,543,296; hereinafter, "Sobol"). Claim 31 has been canceled, thus the rejection with regards to this claim is moot.

Accordingly, withdrawal of rejection of claims 31, 12 and 18-19 and 13 under 35 U.S.C. §103 is respectfully requested.

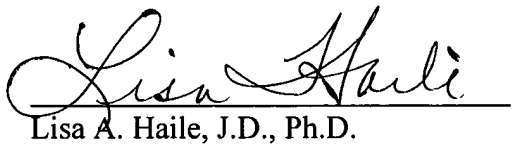
Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the amount of $120.00 is enclosed as payment for the One-Month Petition for Extension of Time. No other fee is deemed necessary with the filing of this paper. However if any fees are due, the Commissioner is hereby authorized to charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: May 8, 2006



Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213